CLINICAL REVIEW 3/26/98

Signature page for PLA 96-1136

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Summary Basis of Approval **Product License Supplement**

Reference Number: 96-1136 Receipt Date: 9/27/96

USAN Name: Filgrastim (rHu G-CSF) Trade Name: Neupogen®

Sponsor: Amgen

Indication: Acceleration of neutrophil recovery in patients undergoing induction and consolidation treatment for acute myeloid leukemia (AML)

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I. Proposed Indication

Neupogen® is indicated for the reduction in the duration of neutropenia, fever, antibiotic use, and hospitalization, in patients undergoing induction and consolidation treatment for acute myeloid leukemia (AML).

II. Clinical Background

The incidence of AML is $1.3/10^5$ in patients <65 years old, and $11.7/10^5$ for those >65 years old, with a median age of 64 years. There are about 7,000 cases per year in the U.S. AML is generally subclassified by the French-American-British (FAB) system into 8 morphologic subtypes, M0-M7:

M0-2	AML with: no (M0), minimal (M1), or significant (M2) maturation
M3	Acute promyelocytic leukemia
M4	Acute myelomonocytic leukemia
M5	Acute monoblastic leukemia
M6	Acute erythroleukemia
M7	Acute megakaryoblastic leukemia

Histologic classification of AML by FAB subtype is useful prognostically and therapeutically. Other prognostic factors which have been reported to correlate with the achievement of complete remission (CR) to standard (cytosine arabinoside-based) induction therapy and survival include: age at diagnosis, performance status, leukocyte count at presentation, presence of Auer rods, and specific chromosomal aberrations.

Patients who have a good prognosis are usually under 45 years of age, with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0, white blood cell count of under 25,000/µl, presence of Auer rods, and FAB classes M3, M2 with t(8;21), or M4 with inv(16)(p13;q22) leukemia. Their CR rate with a cytosine arabinoside-based regimen is about 80%, with a 5 year survival of 50-60%. Factors which contribute to a poor prognosis are age >50-60 years old, ECOG PS of 3-4, white cell count >100,000/µl, absence of Auer rods, and FAB class M0 or M1, M5a with t(9;11)(p22;q23), M5b or M6, or M7 with any of the following karyotypic changes: t(3;3)(q21;q26), -5, -7, 7(7q-), +8, or abnormal 11q23. The CR rate is about 40%, with a 10-30% 5 year survival.

While Filgrastim reduces the duration of neutropenia after chemotherapy for non-myeloid malignancies, the presence of G-CSF receptors on myeloblasts (97% incidence, esp. M3>M1) suggests that there is a risk of G-CSF stimulating the growth of myeloid leukemia. *In vitro*, AML blasts proliferate in response to G-CSF, compared to unstimulated blasts, even though IL-3 and GM-CSF appear to be more potent. Baer et al.[1], have demonstrated that infusions of G-CSF can stimulate leukemic blasts *in vivo*. In 28 untreated patients who received G-CSF at a dose of 10 µg/kg/d IV over 72 hours, 27 patients (96%) showed an increase in the number of circulating or bone marrow blasts. Given this evidence, the use of G-CSF in AML must be evaluated for the risk of decreases in the rate or duration of complete remissions due to stimulation of malignant blasts.

III. Regulatory Background:

Filgrastim, a recombinant methionyl human granulocyte colony stimulating factor, (r-metHuG-CSF), was licensed on February 20, 1991, for use in patients with non-myeloid malignancies receiving myelosuppressive therapy associated with a significant incidence of severe neutropenia with fever. Daily subcutaneous Filgrastim, administered prophylactically, is indicated to shorten the duration of neutropenia and to decrease the incidence of infection as manifested by febrile neutropenia.

Other approved indications are:

1. To reduce the duration of neutropenia and neutropenia-related sequelae (e.g. febrile neutropenia) after autologous bone marrow transplantion (6/15/94)
2. To reduce the incidence and duration of sequelae of neutropenia (e.g. fever, infections, oropharyngeal ulcers) in severe chronic neutropenia (12/19/94)
3. To mobilize hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis (12/28/95)

IV. Summary of Clinical Trials:

The information submitted in this supplemental application consists of the results of a single, randomized, multicenter, placebo-controlled study and literature references. In the review of this supplement, the FDA also considered additional literature references, and the data used to support the use of G-CSF in related clinical conditions.

A. Phase 3 Pivotal Trial

<u>Protocol Synopsis</u>

Title: Protocol GCSF-91134, "A Multicenter, Double Blind, Placebo Controlled, Randomized, Phase 3 Trial of Filgrastim as an Adjunct to Chemotherapy for Acute Myeloid Leukemia"

Dates of accrual 3/92-5/95
Protocol Chair: Dr. Alan Barge

Protocol Design:

This was a double-blind, placebo-controlled, randomized, Phase 3 trial, conducted at 31 centers in Europe and Australia. The patients were stratified by age and center, and randomized to receive either Filgrastim or placebo beginning on Days 6-8 of induction chemotherapy until neutrophil recovery or Day 35.

Objectives:

1° Safety: To determine the effect of G-CSF on remission induction rate.
Efficacy: To determine the effect of G-CSF on the duration of neutropenia.

2° To determine the effect of G-CSF on time to disease progression, and survival time.
To determine the effect of G-CSF on the incidence and duration of fever ($T \geq 38°C$), IV antibiotic use, incidence of documented infection, and duration of hospitalization.

Inclusion criteria:

De novo AML, age ≥16 years
ECOG PS=0-2, life expectancy >6 months, available for followup for 2 years

Exclusion criteria:

Blast transformation of chronic myelogenous leukemia or myelodysplastic syndromes
Prior treatment for AML or 2° AML
Concurrent malignancy or prior cancer other than basal cell or cervical in-situ
Current treatment with other investigational drugs or lithium
Congestive heart failure (NYHA class III-IV)
Prior treatment with colony stimulating factors, interleukins, or interferons
Allergy to E. coli proteins
Addictive or psychiatric disorder
Fecundity, pregnancy, or lactation

Randomization plan:

The randomization schedule, stratified by center and age (<50 or ≥50 years old), was prepared before the start of the study using permuted blocks of size 4-6. Each patient was assigned a unique identification number, corresponding to the next sequential box of study medication for the age group, by the pharmacy or local Amgen office.

Treatment:

All patients were to receive the same induction regimen, DAV 3+7+5, which consisted of daunorubicin 45 mg/m^2 IV on days 1-3, cytosine arabinoside 100 mg/m^2 every 12 hours IV on Days 1-7, and etoposide 100 mg/m^2 IV on Days 1-5. Patients were to be randomized to treatment groups on Day 6, 7, or 8 (near the completion of induction therapy). Study medication was to be administered at 5μg/kg/day subcutaneously, starting 24 hours after the last dose of chemotherapy and continued until the absolute neutrophil count (ANC) recovered to $\geq 1 \times 10^9$/L for 3 consecutive days or $\geq 10 \times 10^9$/L for 1 day, or for a maximum of 35 days (study Day 43, from initiation of chemotherapy), whichever was shorter.

At the time of neutrophil recovery, study medications were to be stopped for 3 days for a bone marrow examination. Patients who failed to achieve a complete remission were to receive a second attempt at remission induction. This regimen, DAV 2+5+5, consisted of daunorubicin 45 mg/m^2 IV on days 1-2, cytosine arabinoside 100 mg/m^2 every 12 hours IV on Days 1-5, and etoposide 100 mg/m^2 IV on Days 1-5.

If remission was achieved (<5% bone marrow myeloblasts after 1-2 courses of induction), patients were to receive 1-2 courses of DAV 2+5+5 consolidation chemotherapy (Consolidation #1 and #2A) followed by study medication. For the second course of consolidation, an alternate regimen (Consolidation #2B) was available for patients under 50 years old, which was given when 4 weeks had elapsed after ANC>1000/µl and platelets>100,000/µl. This alternate regimen consisted of high dose cytosine arabinoside, 3 g/m^2 IV every 12 hours IV on days 1-6, and daunorubicin, 30 mg/m^2 IV on days 7-8.

Prophylactic oral antibiotics (ciprofloxacin/norfloxacin) were to be given from Day 1 until ANC>500/µl. Empiric IV antibiotics were initiated for an oral temperature >38°C, but could be discontinued if the patient defervesced, remained afebrile for 48 hours, and cultures were negative. Patients could be discharged after being afebrile for 72 hours.

Monitoring:

Conventional leukemia care and laboratory tests (e.g. daily blood counts) were to be carried out. Bone marrow examinations were to be performed 2 weeks before chemotherapy and at the time of neutrophil recovery or on Day 43 if neutrophil recovery had not occurred. The protocol required that G-CSF be stopped for a minimum of 3 days before bone marrow assessments. Both the initial and subsequent bone marrow specimens were to be reviewed by a central laboratory.

Endpoints:

The endpoints were considered to be the same as the objectives stated above. In September, 1992, the duration of neutropenia (ANC<500/µl) was made the sole primary efficacy endpoint, and fever was downgraded to a secondary one.

Analytic plan:

A sample size of 400 patients was chosen, based on the assumption that the placebo remission rate would be 65%, and a desire to detect a 15% decrease in the remission rate for G-CSF treated patients, with 90% power and α=0.05. To permit early detection of a major, negative impact on remission rate in the experimental arm, interim safety analyses were to be performed after each 60 patients in A/B blinded format by an independent data monitoring committee for remission rate, progression, and survival.

After data collection was complete, an intent-to-treat approach was to be used with statistical tests for significance. For the primary safety analysis of remission rate, the PEST (Planning and Evaluation of Sequential Trials) software package was to be used to calculate the significance of the differences between the two groups. Times to disease progression were to be shown in Kaplan-Meier plots, and compared by the log-rank test. For the primary efficacy variable of duration of neutropenia, the intergroup comparisons were to be made by the

Hodges-Lehmann estimate and the Wilcoxon rank-sum tests.

Results:

A total of 521 patients were enrolled over 3 years: 259 were randomized to Filgrastim, and 262 to placebo. The median age was 54 years in both arms (ranges >16-89 and >16-88, respectively). All other baseline entry variables also appeared to be well balanced between the two study arms (Table 1).

TABLE 1
COMPARABILITY OF STUDY ARMS FOR BASELINE ENTRY VARIABLES

Baseline entry variables		Filgrastim (n=259)	Placebo (n=262)
Age	<50 y.o.	104 (40%)	115 (44%)
	≥50 y.o.	155 (60%)	147 (56%)
Median (range)		54 (16-89)	54 (16-88)
Gender	M	141 (54%)	142 (54%)
	F	118 (46%)	120 (46%)
WBC, median x 10^9/L (range)		12.0 (0.3-500)	10.0 (0.4-354)
	<25,000/ml	172 (66%)	167 (64%)
	>100,000/ml	26 (10%)	27 (10%)
FAB subtype†	M0	3%	3%
	M1	21%	23%
	M2	27%	24%
	M3	1%	3%
	M4	24%	27%
	M5	17%	13%
	M6	4%	4%
	M7	1%	2%
	Not assessed	2%	1%
Cytogenetics	Normal/favorable	104 (40%)	123 (47%)
	Unfavorable	78 (30%)	75 (29%)
	Not assessed	77 (30%)	64 (24%)
ECOG Performance Status			
Median (range)		1 (0-3)	1 (0-2)
	PS 0	63 (24%)	66 (25%)
	PS 1	152 (59%)	149 (57%)
	PS 2	43 (17%)	47 (18%)
	PS 3	1 (<1%)	0

† The diagnosis of AML was not confirmed by central pathology review in 2 patients in the

G-CSF arm and 7 patients in the placebo arm.

The total population in the intent-to-treat analysis consisted of 521 subjects who were registered and randomized. Of these, 4 subjects in the G-CSF arm and 2 in the placebo arm never received study medication. Ultimately, 7 double triangular analyses of group sequential design were performed in A/B blinded format to preserve the integrity of the tests. The outcome of patients in both arms was very similar, with 69% and 68% achieving remission after one or two attempts in the G-CSF and placebo arms, respectively. The percentages of patients who had persistent disease or died during induction were 21% and 10% respectively in the G-CSF arm, and 22% and 10% in the placebo arm. The majority of subjects (91% of G-CSF and 89% of placebo-treated subjects) who achieved remission went on to receive at least one cycle of consolidation. The second cycle of consolidation was optional; approximately half of the subjects who received the first cycle of consolidation went on to receive a second cycle.

Reasons for failure to complete two cycles of consolidation included early relapse (12 subjects (7%) in the G-CSF arm and 5 (3%) in the placebo), deaths (3 subjects in the G-CSF arm and 4 in the placebo), withdrawal due to unacceptable toxicity (3 subjects in the G-CSF arm and 1 in the placebo), and withdrawal of consent (2 subjects in the placebo arm). Most patients going to bone marrow transplant did so after a second consolidation.

TABLE 2
COMPLETION OF TREATMENT PROGRAM

Phase of treatment	Filgrastim (# of subjects)	Placebo (# of subjects)
Registered and randomized - Induction 1	259	262
Received study drug - Induction 1	255	260
Received Induction 2	60	67
Outcome after Induction 1+2		
Complete remission	178 (69%)	177 (68%)
Persistent disease	54 (21%)	57 (22%)
Death	21 (8%)	25 (10%)
Received Consolidation 1	162	157
Received Consolidation 2 (2A/2B)	60/21	58/26

Protocol violations:

Although compliance with the protocol was high, there were violations which may have had an impact on the assessment of the endpoints. There were 82 violations (involving 44 subjects in the G-CSF and 30 in the placebo arm), which included failure to meet eligibility criteria (n=11, including 9 subjects who did not have AML), 26 patients randomized too early (before study day 5) or too late (after study day 8), errors in study medication in 34 subjects, and variation from the prescribed chemotherapy regimen (n=11). Most violations were similarly distributed between arms but there was a greater number of ineligible subjects without AML in the placebo arm (7 vs. 2 in the G-CSF arm), but this difference did not affect the results significantly.

Among the secondary endpoints, IV antibiotics were continued in many afebrile patients beyond the 48 hours specified in the protocol, but the sponsor called this a violation only if it lasted >4 days. It occurred more frequently in the placebo arm (80 subjects) compared to the G-CSF arm (58 subjects).

Primary Endpoint Analyses

Analysis of the primary safety endpoint of remission induction showed a complete remission rate of 69% for patients randomized to Filgrastim, compared to 68% for placebo patients (p=0.77). The 95% confidence interval around the treatment difference was -6.8% to 9.2% (i.e., the 95% lower confidence limit for the difference between G-CSF and placebo includes a remission rate of 61%). There was no difference between arms in the CR rates for either Induction 1 or 2. The primary efficacy endpoint also was met because the median duration of neutropenia was reduced by 5 days in G-CSF treated patients as compared to placebo-treated patients.

TABLE 3
PRIMARY SAFETY AND EFFICACY ENDPOINTS

Primary Endpoints	Filgrastim n=259	Placebo n=262	Treatment Difference (95% CI)	P-value
Complete Remission Rate	178 (69%)	177 (68%)	1.2% (-6.8%, 9.2%)	0.77*
Median duration of neutropenia (days)	14.0	19.0	-5.0 (-6.0, -4.0)†	0.0001‡

* Fisher's Exact test
† Hodges-Lehmann estimate
‡ Wilcoxon Rank Sum test

Secondary Efficacy Analyses

There were no differences in the incidences of fever, documented infection, or IV antibiotic use, between the two study arms. The median duration of fever was reduced by 1.5 days in the G-CSF arm compared to placebo (7.0 vs. 9.0 days, p=0.009, by Wilcoxon rank sum test). An initial analysis showed that the median duration of parenteral antibiotics was reduced by 3.5 days (15.0 vs. 19.0 days); however, protocol violations of extended use occurred as mentioned above. Since no adjustment back to a 48 hour timepoint could be made, the sponsor performed another analysis which excluded these patients, and found similar results (18 vs. 15 days, p=0.007). A similar problem occurred for the median duration of hospitalization, which was shorter by 5 days in G-CSF compared to placebo-treated patients (20 vs. 25 days). Adjustments could not be made for early deaths, which may have created imbalance between study arms, but when subjects who died in induction were excluded, the durations were 21 days for Filgrastim, and 26 days for placebo (p=0.0001) in 239 patients per arm.

TABLE 4
SECONDARY EFFICACY ENDPOINTS

Variables	Filgrastim (n=259)	Placebo (n=262)	Treatment Difference (95% CI)	P-value
Incidence of fever, T≥38°C	235 (91%)	242 (92%)	-1.6% (-6.4%, 3.1%)	0.532*
Median duration of fever (days)	7.0	8.5	-1.5 (-3.0, 0.0)†	0.009‡
Incidence of non-prophylactic IV antibiotics	247 (95%)	251 (96%)	-0.5% (-4.0%, 3.1%)	0.834*
Median duration of non-prophylactic IV antibiotics (days)	15.0	18.5	-3.5 (-5.0, -2.0)†	0.0001‡
Incidence of documented infections	96 (37%)	95 (36%)	0.8% (-7.5%, 9.1%)	0.856*
Median duration of hospitalization (days)	20.0	25.0	-4.0 (-6.0, -3.0)†	0.0001‡

* Fisher's Exact test
† Hodges-Lehmann estimate
‡ Wilcoxon Rank Sum test

The relative importance of the primary and secondary endpoints was assessed by multivariable analysis. All effects were listed by Amgen in descending order of the strength of correlation: The treatment center, baseline neutropenia, documented baseline infection, and use of G-CSF were significantly associated with the duration of fever. Baseline IV non-prophylactic antibiotics, center, baseline neutropenia, and G-CSF treatment were significantly correlated with the duration of IV antibiotics. For the duration of hospitalization, the treatment center and G-CSF treatment were equally important, followed by prophylactic IV antibiotics, and equivalent factors of baseline neutropenia or baseline infection. The treatment center, baseline IV antibiotics, and age were significantly associated with the incidence of infections. Since the center (study site) tended to be more strongly correlated with the secondary efficacy variables than use of G-CSF, local practice may have influenced greatly the durations of antibiotic use and hospitalization in the absence of well-defined, detailed, and uniform procedures.

Secondary Safety Analyses

The median time to progression was shorter at 165 days for Filgrastim vs. 186 days for placebo (p=0.87). The median overall survival was also shorter at 380 days in the Filgrastim arm vs. 425 days for placebo (p=0.83). In a multivariate analysis, achieving complete remission was the variable most strongly correlated with survival, followed by age, ECOG performance status, and FAB subtype. Use of G-CSF was not correlated with survival in the multivariate analysis.

TABLE 5
SECONDARY SAFETY ENDPOINTS

Variables	Median (95% confidence interval)*		P-value	Difference (95% confidence interval)
	Filgrastim	Placebo		
Time to disease progression (days)	165 (133, 237)	186 (154, 233)	0.87**	-21 (-77, 47)
Survival time (days)	380 (331, 438)	425 (372, 475)	0.83**	-45 (-107, 27)

* Kaplan-Meier estimate
** Log-Rank test

Overall Safety:

Adverse events (AEs) due to Filgrastim are described in the package insert, and no novel toxicities were observed in this trial. There were many serious, life-threatening, and fatal adverse events, but attribution to Filgrastim is difficult due to the nature of the disease and background toxicity of the treatment. In general, the overall toxicity profile was similar between the two arms. Adverse events reported more frequently in patients in the Filgrastim arm during induction included diarrhea (18% vs. 14%), petechiae (17% vs. 14%), purpura (3% vs. 1%), epistaxis (9% vs. 5%), transfusion reaction (7% vs. 1%).

A severe adverse event (SAE) was defined as an adverse event with a WHO toxicity Grade 3 or 4, or one which was serious, life-threatening, or fatal. In general, there were no significant differences in SAEs between the two arms over the entire treatment period, with one exception, the incidence of hemorrhagic events. During the first course of remission induction, the number of patients with serious hemorrhagic events was 7% (19 of 259) for Filgrastim and 2% (5 of 262) for placebo. The following types of hemorrhagic events were reported more frequently in the Filgrastim arm vs. placebo (as number of patients): cerebral hemorrhage (5 vs. 1), pulmonary hemorrhage (3 vs. 0), hematuria (2 vs. 1), ocular hemorrhage (1 vs. 0), epistaxis (2 vs. 0), hemorrhage (1 vs. 0), petechiae (3 vs. 1), thrombocytopenia (2 vs. 0). The following hemorrhagic events were more frequent in placebo patients: hemoptysis (0 vs. 1), hemorrhagic gastric ulcer (0 vs. 1), hemorrhagic pancreatitis (0 vs. 1), hematoma (0 vs. 1). During the second remission induction attempt, 2 patients in the Filgrastim arm were reported to have gastrointestinal hemorrhage, and one in the placebo arm was reported to have hemorrhage (not otherwise specified).

TABLE 6
SEVERE ADVERSE EVENTS BY COURSE

Treatment Course	Filgrastim, #patients/total (%)	Placebo, #patients/total (%)
Induction 1	68/259 (26%)	56/262 (21%)
Induction 2	9/60 (15%)	9/67 (13%)
Consolidation 1	10/162 (6%)	3/157 (2%)
Consolidation 2A	2/60 (3%)	5/58 (9%)
Consolidation 2B	7/21 (33%)	10/26 (38%)

Serious, life-threatening, but non-fatal events are tabulated below. Three respiratory events (bronchospasm, hypoxia, and pulmonary edema) were thought to be related to Filgrastim, whereas pneumonia (6 G-CSF vs. 2 placebo), ARDS, dyspnea/respiratory failure, and hemothorax were felt to be unrelated. In the hematologic system, leukemia progression or relapse was reported in 6 G-CSF vs. 3 placebo patients. The cardiovascular events were angina, congestive heart failure, ventricular fibrillation, or venous thrombosis.

TABLE 7
SERIOUS, NON-FATAL ADVERSE EVENTS

	Filgrastim, n = 259	Placebo, n = 262
Number of events	45	36
Number of patients (%)	41 (16%)	31 (12%)

Body system	Number of patients (%)	Number of patients (%)
Respiratory	13 (5%)	4 (2%)
Hematologic	7 (3%)	5 (2%)
Cardiac + vascular	3 (1%)	1 (<1%)

There were 15 Filgrastim patients and 16 placebo subjects who withdrew due to adverse events. The reasons given for the G-CSF arm included cardiovascular (angina, heart failure, vasculitis), gastrointestinal (bleeding), neurologic (cerebral hemorrhage), pulmonary (bronchospasm, respiratory failure), septic shock, and hematologic (relapse, monocytosis, neutropenia, and Sweet's syndrome, a condition of febrile neutrophilic dermatosis associated with pulmonary infiltrates.)

Thirty Filgrastim patients and 32 placebo patients died after randomization and before the end of the data collection period on 6/30/95. In some cases, the causes were straightforward, and attribution was simple; however, in many instances, the etiology was multifactorial. If persistent disease was present, this was assigned as the cause. If not, the distinction between infection and coagulopathy when both were present was made on the basis of the neutrophil and platelet counts at the time of death.

TABLE 8
MORTALITY

Deaths on Study	Filgrastim (n=259)	Placebo (n=262)
During induction (1+2)	22 (8%)	25 (10%)
Infection-related	7	10
Hemorrhage	6	3
Persistent disease	6	12
Other (renal failure x2, cardiotoxicity)	3	0
Refractory disease	3 (1%)	2 (1%)
In remission	4 (2%)	5 (2%)
Infection	3	3
Hemorrhage	1	2
After relapse (heart disease, pulmonary edema)	1 (0%)	0 (0%)
Total	30 (12%)	32 (12%)

Two patient deaths were reported to be possibly related to study medication: Patient [redacted] (G-CSF) died in induction due to leukemia, pulmonary edema, and ileus. Patient [redacted] (G-CSF) was in remission after induction, but relapsed after the first consolidation course, and died due to leukemia, coronary artery disease, and pulmonary edema. The causes of death with chemotherapy in AML are usually multifactorial, and it is often difficult to assign a single cause.

Exploratory analyses:

1. Analyses were performed to assess the consistency of effect of G-CSF over multiple courses of dose-intensive chemotherapy. For comparison with the primary efficacy endpoint, the time to neutrophil recovery (ANC>500) was tabulated from the start of study medication, rather from the initiation of the chemotherapy cycle. Except for Induction 2, the time to neutrophil recovery is consistently shorter in the G-CSF-treated arm over multiple cycles of induction and consolidation chemotherapy:

TABLE 9
DURATION OF NEUTROPENIA IN INDUCTION AND CONSOLIDATION

Course of chemotherapy	Filgrastim		Placebo		p-value
	n	Median days to ANC<500 (range)	n	Median days to ANC<500(range)	
Induction 1	259	14 (0-38)	262	19 (4-40)	0.0001§
Induction 2	60	10	67	14	0.015
Consolidation 1	162	4	157	11	0.0001
Consolidation 2A	60	5	58	10	0.0001
Consolidation 2B	21	13	26	18.5	0.001

§Hodges-Lehmann estimate; other p-values by Wilcoxon rank-sum tests.

An analysis of the incidence of febrile neutropenia, defined as any event in which both a temperature of 38°C or higher was observed in a subject with an ANC<500/μl, was performed to further assess the clinical relevance of reduction in duration of fever. While the incidence of febrile neutropenia was not reduced in G-CSF treated patients during the first induction course, it was significantly lower during Consolidation 1 and 2A. The latter two courses both employed the DAV 2+5+5 regimen as Induction 2, so the difference in outcomes may be attributable to the underlying disease:

TABLE 10
COMPARISON OF INCIDENCE OF FEBRILE NEUTROPENIA BY COURSE

Chemotherapy course	Filgrastim	Placebo	p-value
	Incidence of febrile neutropenia	Incidence of febrile neutropenia	

Induction 1	232/259 (90%)	241/262 (92%)	0.3
Induction 2	47/60 (78%)	48/67 (72%)	0.4
Consolidation 1	51/162 (32%)	73/157 (47%)	0.007
Consolidation 2A	16/60 (27%)	31/58 (53%)	0.003
Consolidation 2B	19/21 (90%)	23/26 (88%)	0.8

2. Since age is a prognostic variable, and Sargramostim (GM-CSF) has been shown to improve survival in elderly patients >55-70 years old with primary AML, a post-hoc analysis was performed to evaluate the effect of G-CSF on efficacy variables, remission rate (CR), time to progression (TTP), and overall survival (OS) of patients ≤55 or >55 years old. No significant differences in response to Filgrastim based on age were found:

TABLE 11
COMPARISON OF OUTCOMES FOR ≤55 or >55 YEARS OF AGE

	Age ≤55		Age >55	
Outcomes	G-CSF n=139	Placebo n=137	G-CSF n=120	Placebo n=125
1° and 2° Efficacy Endpoints (Induction 1, median duration in days)				
Neutropenia*	19	24	20	24
Fever**	6	8	8	9
Antibiotic use*	15	19	14	18
Hospitalization*	20	23	20.5	26
Safety Endpoints (95% Confidence Intervals)				
CR rate (Induction 1)	73% (101/139)	69% (95/137)	64% (77/120)	66% (82/125)
Median TTP (days)	203 (139, 297)	253 (182, 321)	139.5 (82, 240)	154 (124, 192)
Median OS (days)	409 (368, 598)	491 (426, 646)	345 (192, 423)	349 (246, 414)

* Significant at $p<0.05$ by Wilcoxon Rank Sum test for all pairwise comparisons (≤55, >55 y.o.)
** Significant at $p<0.05$ only for the ≤55 y.o. group

It is interesting, but problematic, to compare the results of Filgrastim in AML patients over 55 years to the Phase 3 trial of Sargramostim by Rowe et al. (Blood, 86:457-462, 1995). A major difference in the latter protocol was that a BM exam was done at the end of induction chemotherapy, and patients were eligible only if they had <5% blasts. While not meeting the full criteria for CR (the marrow was hypoplastic), this late randomization was likely to exclude patients with persistent disease and early mortality. Nevertheless, the CR rate with G-CSF was higher than for GM-CSF, and the median overall survival times were similar. However, unlike the Rowe study, no benefit in overall survival was seen with Filgrastim compared to the placebo arm. Much of the benefit of GM-CSF seemed to be due to a lower incidence of infectious deaths during induction chemotherapy, whereas in the G-CSF study, all patients received prophylactic antibiotics, and the early death rate from infection was low in both arms.

TABLE 12
RESPONSE RATES AND SURVIVAL FOR PATIENTS >55 YEARS OF AGE

Outcomes	G-CSF n=120	Placebo n=125	GM-CSF n=60	Placebo n=57
CR rate	64% (77/120)	66% (82/125)	60% (36/60)	44% (25/57)
Median OS	345 days	349 days	342 days	268 days

B. Relevant literature references

Six studies from the published literature were reviewed in support of the proposed indication.

1. Ohno et al.[2] studied 78 primary or secondary AML patients in an open-label, randomized study. Kirin G-CSF at 200μg/m^2/d was started 2 days after chemotherapy. The time to neutrophil recovery (ANC>500/μl) was 20 days vs. 28 days for G-CSF vs. placebo ($p = 0.0002$), and the time to ANC>1000/μl was 22 days vs. 34 days. The incidence of proven infections was 19% vs. 45% (G-CSF vs. placebo, $p = 0.028$) and the complete remission rates were 50% in the G-CSF arm and 36% in the placebo arm (not significant). There was no difference in relapse rate.

2. Baer et al.[3] studied 20 patients with primary AML and 10 patients with secondary AML in an uncontrolled Phase 2 study. G-CSF 10μg/kg/d was started 24 hours after chemotherapy. The time to neutrophil recovery (ANC>500/μl) was 20 days from Day 1 of chemotherapy. There were 58% Grade 3-5 infections. The complete remission rate was 65% for primary AML, 40% for patients >60 y.o. and 20% for secondary AML. 64% of patients developed hyperbilirubinemia.

3. Ohno et al.[4] also studied patients with relapsed or refractory AML. This was a randomized, double-blind trial in which study drug was started 2 days before chemotherapy. 28 patients were treated with G-CSF, and 30 were on the placebo arm. The time to neutrophil recovery (ANC>500/μl) was 24 days vs. 29 days (G-CSF vs. placebo, $p = 0.0006$), and the time to ANC>1000/μl was 25 days vs. 32 days (p =

0.0018). The incidence of fever and infections was similar in each arm. The complete remission rate was 50% for the G-CSF group, and 37% for the placebo group, but this difference was not significant, and there was no difference in the disease-free survival of about 7 months for either arm.

4. Dombret et al.[5] reported 173 patients 65 years of age with *de novo* AML in a randomized, double-blind study. After induction, the patients' bone marrow was examined before lenograstim, 5µg/kg/d, which was given from Day 9 up to Day 28. The time to neutrophil recovery (ANC>1000/µl) was 21 days vs. 27 days for G-CSF patients vs. placebo patients (p = 0.001), and there was no difference in infection. The complete remission rate was 70% for the G-CSF arm vs. 47% for the placebo arm (p = 0.002), but the overall survival was 8 vs. 6 months respectively (not significant). About 8% of patients had increased blasts in the G-CSF arm.

5. Godwin et al.[6] studied primary or secondary AML patients in a randomized, double-blind trial of 68 G-CSF patients and 79 placebo patients, who had to be in bone marrow remission before study medication was given on Day 11.They found that time to neutrophil recovery (ANC>500/µl) was 3-5 days faster with G-CSF, which also decreased median fever duration from 10 days to 7 days, and antibiotic use from 26 days to 22 days, but there was no difference in hospital days. The complete remission rate was 42% with G-CSF vs. 49% for placebo. In seondary AML, the complete remission rate was only 5% with G-CSF vs. 33% for placebo, but this was not significant. The overall survival was 5 months for G-CSF vs. 9 months for placebo, but this also was not significant.

6. Maslak et al[7] studied 26 patients, over 60 years old with *de novo* AML, and compared them to historical controls. G-CSF, 10µg/kg, was given by continuous IV started 24 hours after chemotherapy. The time to neutrophil recovery (ANC>500/µl) as measured from Day 1 of G-CSF, rather than of chemotherapy was 13 days vs. 17 days (G-CSF vs. placebo, p = 0.008), and the time to ANC>1000/µl was 14 days vs. 19days (p = 0.005). There was a 73% documented infection rate. The complete remission rate was 71%, and the toxic death rate was (8% vs. 32%, p=0.04). There was no difference in disease-free or overall survival.

These studies uniformly support the claim that G-CSF shortens the duration of neutropenia in AML, but the evidence is conflicting on its ability to decrease fever, infections, or antibiotic use. There appears to be no significant effect on overall survival.

C. Relevant Data from Other PLAs

Filgrastim was approved in February, 1991, for non-myeloid cancer patients receiving myelosuppressive chemotherapy. It is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever. In several clinical studies, Filgrastim has been shown to be safe and effective in accelerating the recovery of neutrophil counts following a variety of chemotherapy regimens.

In a Phase 3, randomized, double-blind, placebo-controlled trial, patients with small cell lung cancer were randomized to receive Filgrastim (n = 99, 4 to 8 mcg/kg/day subcutaneously) or placebo (n = 111) on days 4-17, after receiving standard dose chemotherapy with cyclophosphamide, doxorubicin, and etoposide. The Filgrastim was discontinued when the absolute neutrophil count (ANC) was $\geq 10{,}000/mm^3$ after the expected chemotherapy-induced nadir. A total of 210 patients were evaluated for efficacy and 207 evaluated for safety. Treatment with Filgrastim resulted in a clinically and statistically significant reduction in the incidence of infection, as manifested by febrile neutropenia; the incidence of at least one infection over all cycles of chemotherapy was 76% (84/111) for placebo-treated patients, versus 40% (40/99) for Filgrastim-treated patients ($p<0.001$).

The following secondary analyses were also performed. The requirements for in-patient hospitalization and antibiotic use were also significantly decreased during the first cycle of chemotherapy; incidence of hospitalization was 69% (77/111) for placebo-treated patients in cycle one, versus 52% (51/99) for Filgrastim-treated patients ($p=0.032$). The incidence of intravenous antibiotic usage was 60% (67/111) for placebo-treated patients in cycle one, versus 38% (38/99) for Filgrastim-treated patients ($p=0.003$).

The incidence, severity, and duration of severe neutropenia ($ANC < 500/mm^3$) following chemotherapy were all significantly reduced. The incidence of severe neutropenia in cycle one was 84% (83/99) for patients receiving Filgrastim versus 96% (106/110) for patients receiving placebo ($p=0.004$). Over all cycles, patients randomized to Filgrastim had a 57% (286/500 cycles) rate of severe neutropenia versus 77% (416/543 cycles) for patients randomized to placebo. The median duration of severe neutropenia in cycle 1 was reduced from 6 days (range 0-10 days) for patients receiving placebo to 2 days (range 0-9 days) for patients receiving Filgrastim ($p < 0.001$). The mean duration of neutropenia in cycle 1 was 5.64 ± 2.27 days for patients receiving placebo versus 2.44 ± 1.90 days for patients receiving Filgrastim. Over all cycles, the median duration of neutropenia was 3 days for patients randomized to placebo versus 1 day for patients randomized to Filgrastim.

Several other Phase 1/2 studies, which did not directly measure the incidence of infection, but which did measure increases in neutrophils, supported the efficacy of Filgrastim in the setting of myelosuppressive chemotherapy.

2. Filgrastim was subsequently approved in June, 1994, for cancer patients receiving autologous bone marrow transplantation. In two separate randomized, controlled trials, patients with Hodgkin's and non-Hodgkin's lymphoma were treated with myeloablative chemotherapy and autologous bone marrow transplantation (ABMT). In one study (n=54), Filgrastim was administered at doses of 10 or 30 μg/kg/day; a third treatment group in this study received no Filgrastim. A statistically significant reduction in the

median number of days of severe neutropenia (ANC<500/mm^3) occurred in the Filgrastim-treated group versus the control group (23 days in the control group, 11 days in the 10 μg/kg/day group, and 14 days in the 30 μg/kg/day group, (11 days in the combined treatment groups, p = 0.004)).

In the second study (n=44, 43 patients evaluable), Filgrastim was administered at doses of 10 or 20 μg/kg/day; a third treatment group in this study received no Filgrastim. A statistically significant reduction in the median number of days of severe neutropenia occurred in the Filgrastim-treated group versus the control group (21.5 days in the control group and 10 days in both treatment groups, p <0.001). The number of days of febrile neutropenia was also reduced significantly in this study [13.5 days in the control group, 5 days in the 10 μg/kg/day group, and 5.5 days in the 20 μg/kg/day group, (5 days in the combined treatment groups, p<0.0001)]. Reductions in the number of days of hospitalization and antibiotic use were also seen, although these reductions were not statistically significant. There were no effects on red blood cell or platelet levels.

In a randomized, placebo-controlled trial, 70 patients with myeloid and non-myeloid malignancies were treated with myeloablative therapy and allogeneic bone marrow transplant followed by 300 μg/M^2/day of a Filgrastim product. A statistically significant reduction in the median number of days of severe neutropenia occurred in the treated group versus the control group (19 days in the control group and 15 days in the treatment group, p<0.001) and time to recovery of ANC to ≥500/mm^3 (21 days in the control group and 16 days in the treatment group, p<0.001).

In three non-randomized studies (n=119), patients received ABMT and treatment with Filgrastim. One study (n=45) involved patients with breast cancer and malignant melanoma. A second study (n=39) involved patients with Hodgkin's disease. The third study (n=35) involved patients with non-Hodgkin's lymphoma, acute lymphoblastic leukemia (ALL), and germ cell tumor. In these studies, the recovery of the ANC to ≥500/mm^3 ranged from a median of 11.5 to 13 days.

None of the conditioning regimens used in the ABMT studies included radiation therapy. While these studies were not designed to compare survival, this information was collected and evaluated. The overall survival and disease progression of patients receiving Filgrastim in these studies were similar to those observed in the respective control groups and to historical data.

VI. Conclusions:

There is extensive experience with Filgrastim in myelosuppressive chemotherapy and hematopoietic cell transplantation. With AML, there has been a theoretical concern about the use of a myeloid growth factor following chemotherapy. G-CSF has been observed to stimulate myeloblasts in patients, with the risk of lower remission and higher relapse rates. This may be offset by recruitment (priming) of malignant cells to become sensitive to cycle-specific agents, although studies of G-CSF as a priming agent are inconclusive.

In the single, randomized, placebo-controlled clinical trial submitted in this application, Filgrastim significantly decreased the duration of neutropenia, the duration of fever, and pending confirmation, the duration of intravenous antibiotic use and hospitalization. This trial was sized to detect a 15% worsening in the CR rate, and none was found, since the lower bound of the 95% confidence interval for the difference in remission rate between the two study arms was -6.8%. The times to disease progression and overall survival also were not significantly different, although the values were lower for the G-CSF patients.

The data for the use of GM-CSF (Sargramostim, Leukine®) support the safety of that growth factor in older patients with AML. There were, however, some significant benefits observed with Sargramostim which were not seen with Filgrastim. The former agent significantly improved overall survival, and significantly reduced deaths during induction, primarily due to a decrease in documented infections and infectious deaths. However, the two trials cannot be compared readily, as there were major differences in the protocols, e.g., the populations studied, the chemotherapy regimens administered, and timing of the growth factor. The Filgrastim study was much larger than the Sargramostim trial, and was conducted in a wider age range. The chemotherapy also differed, and may have affected remission rate and overall survival. Finally, in the Sargramostim trial, a bone marrow examination was performed after induction chemotherapy, and patients were randomized only if they had <5% blasts. At this time point, randomization may have excluded patients with persistent disease and poor survival. In the Filgrastim study, the omission of a bone marrow examination prior to growth factor administration did not pose an excessive risk.

VII. References

1. Baer et al., Blood 87:1484-94, 1996
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